Complete Summary

GUIDELINE TITLE

Guidelines for the use of antiretroviral agents in pediatric HIV infection.

BIBLIOGRAPHIC SOURCE(S)

Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the use of antiretroviral agents in pediatric HIV infection. Bethesda (MD): U.S. Department of Health and Human Services; 2008 Feb 23. 139 p. [460 references]

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the use of antiretroviral agents in pediatric HIV infection. Bethesda (MD): U.S. Department of Health and Human Services; 2008 Jul 29. 134 p.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- July 24, 2008, Ziagen (abacavir sulfate): The U.S. Food and Drug Administration (FDA) has notified the maker of abacavir and abacavir-containing medications of the need to add information to the current BOXED WARNING about the recommendation to test all patients for the HLA-B*5701 allele before starting or restarting therapy with abacavir or abacavir-containing medications.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Human immunodeficiency virus (HIV) infection
- Acquired immunodeficiency syndrome (AIDS)

GUIDELINE CATEGORY

Counseling
Diagnosis
Evaluation
Management
Prevention
Risk Assessment
Screening
Treatment

CLINICAL SPECIALTY

Allergy and Immunology
Family Practice
Infectious Diseases
Internal Medicine
Pediatrics

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Clinical Laboratory Personnel
Health Care Providers
Health Plans
Hospitals
Nurses
Pharmacists
Physician Assistants
Physicians
Public Health Departments

GUIDELINE OBJECTIVE(S)

To update the existing antiretroviral treatment guidelines for children and to provide guidelines for the antiretroviral treatment of human immunodeficiency

virus (HIV)-infected infants, children, and adolescents similar to those for HIV-infected adults

TARGET POPULATION

Infants, children, and pre-pubertal adolescents at risk for or infected with human immunodeficiency virus (HIV) in the United States

INTERVENTIONS AND PRACTICES CONSIDERED

Evaluation/Diagnosis/Prevention

1. Maternal prenatal testing and counseling
2. Identification of perinatal human immunodeficiency virus (HIV) exposure
3. Diagnosis of HIV in infants (HIV deoxyribonucleic acid [DNA] and ribonucleic acid [RNA] assays)
4. Laboratory monitoring (CD4 percentage or count, plasma HIV RNA)
5. Maternal counseling regarding breastfeeding

Treatment/Management

1. Consideration of when to begin therapy in antiretroviral naïve children
2. Combination therapy with at least 3 drugs for antiretroviral-naïve children
    - Non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens (1 NNRTI + 2 nucleoside analogue reverse transcriptase inhibitor [NRTI] backbone)
    - Protease inhibitor (PI)-based regimens (1 or 2 PIs + 2 NRTI backbone)
    - Triple NRTI regimens (zidovudine + lamivudine + abacavir, recommended only in special circumstances)

    Note: See the "Major Recommendations" and the original guideline document for detailed information about preferred and alternative regimens, as well as regimens to use only in special circumstances and those that are not recommended.

3. Monitoring of children on antiretroviral therapy for side effects (including growth and development), response to therapy, and adherence to regimen
4. Consideration of specific issues in antiretroviral therapy for HIV-infected adolescents (including drug formulations and drug interactions)
5. Strategies to maximize adherence to therapy
6. Management of medication toxicity or intolerance
7. Management of antiretroviral treatment failure
    - Assessment of antiretroviral treatment failure
    - Management of antiretroviral treatment failure
    - Choosing the next antiretroviral regimen for treatment failure with evidence of drug resistance
    - Use of antiretroviral agents not approved for use in children
    - Therapeutic drug monitoring
    - Discontinuation or interruption of therapy
8. Antiretroviral drug resistance testing, including viral genotype, phenotype and coreceptor (tropism) assays
9. Management of complications of HIV infection
10. Consultations with a pediatric HIV specialist

MAJOR OUTCOMES CONSIDERED

- Transmission rate to infants
- Virologic response to antiretroviral therapy as measured by human immunodeficiency virus (HIV) ribonucleic acid (RNA) levels and immunologic response as measured by CD4 lymphocyte count/percent
- Disease progression based on virologic (HIV RNA load), immunologic (CD4+ cell count), or clinical (progressive neurodevelopmental deterioration, growth failure) parameters
- Toxicities of antiretroviral therapy
- Drug/treatment failure due to toxicities
- Drug resistance
- Mortality rates
- Rates of opportunistic infections and other complications of HIV infection
- Adherence
- Quality of life
- Physical growth
- Neurocognitive development

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

There are few randomized, phase III clinical trials of highly active anti-retroviral therapy (HAART) among pediatric patients that provide direct comparison of different treatment regimens; most pediatric drug data come from phase I/II safety and pharmacokinetic trials and non-randomized, open-label studies. The Working Group reviews both child and adult clinical trial data published in peer-reviewed journals, data prepared by manufacturers for U.S. Food and Drug Administration (FDA) review, and data presented in abstract format at major scientific meetings.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review
Review of Published Meta-Analyses

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

In 1993, the Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children, composed of specialists caring for human immunodeficiency virus (HIV)-infected infants, children, and adolescents, was convened by the François-Xavier Bagnoud Center (FXBC), University of Medicine and Dentistry of New Jersey (http://www.fxbcenter.org). Since 1998, the Working Group has held monthly conference calls to review new data. Proposed changes to the pediatric treatment guidelines are reviewed by the Working Group and incorporated as appropriate.

Concepts Considered in the Formulation of Pediatric Treatment Guidelines

The following concepts were considered in the formulation of these guidelines:

- Prenatal HIV testing and counseling should be the standard of care for all pregnant women in the United States. Identification of HIV-infected women before or during pregnancy is critical to providing optimal therapy for both infected women and their infants and for reduction of perinatal transmission. Access to prenatal care is essential for all pregnant women.
- Enrollment of pregnant HIV-infected women; their HIV-exposed newborns; and infected infants, children, and adolescents into clinical trials offers the best means of determining safe and effective therapies.*
- The pharmaceutical industry and the federal government should continue collaboration that assures that drug formulations suitable for administration to infants and children are available for all antiretroviral drugs produced.
- Although some information regarding the efficacy of antiretroviral drugs for children can be extrapolated from clinical trials involving adults, concurrent clinical trials for children are needed to determine the impact of the drug on specific manifestations of HIV infection in children, including growth, development, and neurologic disease. However, the absence of phase III efficacy trials addressing pediatric-specific manifestations of HIV infection does not preclude the use of any approved antiretroviral drug in children.
- Treatment of HIV infection in infants, children, and adolescents is rapidly evolving and becoming increasingly complex; therefore, wherever possible, their treatment should be managed by a specialist in pediatric and adolescent HIV infection. If this is not possible, such experts should be consulted.

- Effective management of the complex and diverse needs of HIV-infected infants, children, adolescents, and their families requires a multidisciplinary team approach that includes physicians, nurses, dentists, social workers, psychologists, nutritionists, outreach workers, and pharmacists.
- Health care providers considering antiretroviral regimens for infants, children, or adolescents should consider certain factors influencing adherence to therapy, including:
    - Availability and palatability of pediatric formulations
    - Impact of the medication schedule on quality of life, including number of medications, frequency of administration, ability to co-administer with other prescribed medications, and need to take with or without food
    - Ability of the child's caregiver or the adolescent to administer complex drug regimens and availability of resources that might be effective in facilitating adherence
    - Potential for drug interactions
- The choice of initial antiretroviral regimens should include consideration of factors that may limit future treatment options, such as the presence of or potential for the development of antiretroviral resistance. HIV resistance assays have proven useful in guiding initial therapy and in changing failing regimens, but expert clinical interpretation is required.
- Monitoring growth and development, short- and long-term drug toxicities, neurodevelopment, symptom management, and nutrition are all essential in the care of HIV-infected children, as they may significantly influence quality of life; these issues are addressed in Supplement II: Managing Complications of HIV Infection (see "Availability of Companion Documents" field).

*In areas where enrollment in clinical trials is possible, enrolling the child in available trials should be discussed with the caregivers of the child. Information about clinical trials for HIV-infected adults and children can be obtained from the AIDS*info* Web site (http://aidsinfo.nih.gov/) or by telephone at 1-800-448-0440.

Criteria Used for Recommendations of Recommended Regimens for Initial Therapy for Antiretroviral-Naïve Children

Recommendations on the optimal initial therapy for children are continually being modified as new data become available, new therapies or drug formulations are developed, and late toxicities become recognized.

Criteria used by the Working Group for recommending specific drugs or regimens include:

- Data demonstrating durable viral suppression, immunologic improvement, and clinical improvement (when such data are available) with the regimen, preferably in children as well as adults
- The extent of pediatric experience with the particular drug or regimen
- Incidence and types of short- and long-term drug toxicity with the regimen, with special attention to toxicity reported in children
- Availability and palatability of formulations appropriate for pediatric use, including taste, ease of preparation (e.g., powders), volume of syrups, and pill size and number
- Dosing frequency and food and fluid requirements
- Potential for drug interactions

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Recommendations for drugs or drug combinations for use in treatment-naïve children are classified in one of several categories as follow:

- **Preferred**: Drugs or drug combinations are designated as preferred for use in treatment-naïve children when clinical trial data in children or, more often, in adults have demonstrated optimal efficacy and durability with acceptable toxicity and ease of use, and studies have been performed to demonstrate safety and surrogate marker efficacy in children; additional considerations are listed in the original guideline document.
- **Alternative**: Drugs or drug combinations are designated as alternatives for initial therapy when clinical trial data in children or adults show efficacy but there are disadvantages compared to preferred regimens in terms of more limited experience in children; the extent of antiviral efficacy or durability is less well defined in children or less than a preferred regimen in adults; there are specific toxicity concerns; or there are dosing, formulation, administration, or interaction issues for that drug or regimen.
- **Use in Special Circumstances**: Some drugs or drug combinations are recommended only for use in special circumstances, when preferred or alternative drugs cannot be used.
- **Not Recommended**: A list of drugs and drug combinations that are not recommended for initial therapy in children is shown in Table 4 in the original guideline document. These drugs and drug combinations are not recommended either because of inferior virologic response, potential serious safety concerns (including potentially overlapping toxicities), or pharmacologic antagonism.
- **Insufficient Data to Recommend**: There are a number of drugs and drug combinations that are approved for use in adults that do not have pharmacokinetic or safety data available in children, or for which such data are too limited to make a recommendation for use for initial therapy in children. Some of these drugs and drug combinations may be appropriate for consideration in the management of the treatment-experienced child (see Antiviral Treatment Failure in Infants, Children, and Adolescents in the original guideline document).

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

All revisions are summarized and highlighted on the AIDSinfo Web site and posted for a public comment period, generally for 2 weeks, after which comments are reviewed by the Working Group prior to finalization.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Definitions for the classes of recommendations for drugs or drug combinations for use in treatment-naïve children ("Preferred," "Alternative," "Use in Special Circumstances," "Not Recommended," and "Insufficient Data to Recommend") are provided at the end of the Major Recommendations field.

Note from the National Guideline Clearinghouse (NGC): The Department of Health and Human Services updated the "Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection" on February 23, 2009. The following guidelines reflect the current recommendations.

Content Changes

The key changes to the different sections of the guidelines are outlined below:

What Drugs to Start: Initial Combination Therapy for Antiretroviral-Naïve Children

- Although darunavir is recently approved for treatment of infected children over age 6 years, because the currently available formulations require a high pill burden to provide adequate dosing for children weighing under 40 kg and several alternative options are available for initial treatment, darunavir is not currently recommended for initial therapy in children. However, low-dose ritonavir boosted darunavir and tipranavir have utility as components of secondary treatment regimens for children who fail initial therapy.
- Table 7: Updated information on darunavir included.

Antiretroviral Treatment Failure in Infants, Children, and Adolescents

- The former section "Management of the Treatment Experienced Child" has been completely revised into a more detailed section on management of treatment failure in children.
- Definitions of viral and immune failure have been updated.
- A detailed discussion of discordance between viral, immune, and clinical responses has been added.
- A new table (Table 13) on Assessment of Antiretroviral Treatment Failure has been added to provide more explicit guidance on evaluation of a child with treatment failure.
- Revised sections on Approach to the Management of Treatment Failure and Choice of Next Antiretroviral Regimen for Treatment Failure with Evidence of Drug Resistance have been added.
- A new section on the Use of Antiretroviral Agents Not Approved for Use in Children has been added.
- Table 15 has the addition of therapeutic target trough concentrations for maraviroc and tipranavir.

Antiretroviral Drug Resistance Testing

- The section has been updated and includes tropism assays.

Appendix B: Characteristics of Available Antiretroviral Drugs

- Updates have been added for the drugs abacavir, didanosine, lamivudine, stavudine, zidovudine, nevirapine, atazanavir, darunavir, ritonavir, and maraviroc.

Supplement I: Pediatric Antiretroviral Drug Information

- Updates have been added to the overview, and to drug sections on abacavir, didanosine, lamivudine, zidovudine, efavirenz, darunavir, ritonavir, maraviroc, and raltegravir.

Identification of Perinatal Human Immunodeficiency Virus (HIV) Exposure

Working Group Recommendations

- Universal counseling and voluntary HIV testing early in pregnancy, including opt-out testing, is recommended as standard of care for all pregnant women in the United States.
- Repeat HIV testing is recommended in the third trimester for women at high risk of HIV infection who have negative HIV antibody tests earlier in pregnancy.
- Rapid HIV antibody testing is recommended to screen women who are seen at labor and have undocumented HIV status to allow intrapartum antiretroviral prophylaxis to be initiated prior to delivery in women identified as HIV-infected.
- Women who have not been tested for HIV prior to or during labor should be offered rapid testing during the immediate postpartum period or their newborns should undergo rapid HIV antibody testing, with counseling and consent of the mother unless state law allows testing without consent. This allows initiation of antiretroviral prophylaxis soon after delivery for infants born to HIV-infected women, counseling of HIV-infected women not to breastfeed their infant, and linkage to HIV-related medical care and services for both mother and child.

Diagnosis of HIV Infection in Infants

Working Group Recommendations

- Infants under age 18 months require virologic assays that directly detect HIV to diagnose HIV infection, since antibody assays cannot be used due to the persistence of maternal HIV antibody in this age group.
- Virologic diagnostic testing in infants with known perinatal HIV exposure is recommended at age 14 to 21 days; 1 to 2 months; and 4 to 6 months. Some experts also perform virologic testing at birth.
- Preferred virologic assays include HIV deoxyribonucleic acid polymerase chain

reaction (DNA PCR) and HIV ribonucleic acid (RNA) assays.
- Many experts confirm the absence of HIV infection in infants with negative virologic tests by performing an antibody test at age 12 to 18 months to document seroreversion to HIV antibody negative status.
- In children 18 months and older, HIV antibody assays can be used for diagnosis.

Laboratory Monitoring of Pediatric HIV Infection

Working Group Recommendations

- In children under age 5 years, CD4 percentage is preferred for monitoring immune status because of age-related changes in absolute CD4 count in this age group.
- CD4 percentage or count should be measured at the time of diagnosis of HIV infection and at least every 3 to 4 months thereafter.
- Plasma HIV RNA should be measured to assess viral load at the time of diagnosis of HIV infection and at least every 3 to 4 months thereafter.
- More frequent CD4 cell and plasma HIV RNA monitoring may be considered in infants less than age 6 to 12 months; in children with suspected clinical, immunologic, or virologic deterioration; to confirm an abnormal value; or when initiating or changing therapy.
- The age of the child must be considered when interpreting the risk of disease progression based on CD4 percentage or count and plasma HIV RNA level.
- Optimally, the goal of antiretroviral therapy is to reduce plasma HIV RNA levels to below the limits of quantitation on ultrasensitive assays and to normalize immune status.

Treatment Recommendations

General Considerations

A number of factors need to be considered in making decisions about initiating and changing antiretroviral therapy in children, including:

- Severity of HIV disease and risk of disease progression, as determined by age, presence or history of HIV-related or acquired immune deficiency syndrome (AIDS)-defining illnesses (see pediatric clinical staging system for HIV, Table 1 in the original guideline document), level of CD4 cell immunosuppression, and magnitude of HIV plasma viremia
- Availability of appropriate (and palatable) drug formulations and pharmacokinetic information on appropriate dosing in the child's age group
- Potency, complexity (e.g., dosing frequency, food and fluid requirements), and potential short- and long-term adverse effects of the antiretroviral regimen
- Effect of initial regimen choice on later therapeutic options
- Presence of comorbidity that could affect drug choice, such as tuberculosis, hepatitis B or C virus infection, or chronic renal or liver disease

- Potential antiretroviral drug interactions with other prescribed, over-the-counter, or alternative medications taken by the child
- The ability of the caregiver and child to adhere to the regimen

The following recommendations provide general guidance for decisions related to treatment of HIV-infected children, and flexibility should be exercised according to a child's individual circumstances. Guidelines for treatment of HIV-infected children are evolving as new data from clinical trials become available. Although prospective, randomized, controlled clinical trials offer the best evidence for formulation of guidelines, most antiretroviral drugs are approved for use in pediatric patients based on efficacy data from clinical trials in adults, with supporting pharmacokinetic and safety data from phase I/II trials in children. Additionally, efficacy has been defined in most adult trials based on surrogate marker data, as opposed to clinical endpoints. For the development of these guidelines, the Working Group reviewed relevant clinical trials published in peer-reviewed journals or in abstract form, with attention to data from pediatric populations when available.

Goals of Antiretroviral Treatment

The goals of antiretroviral therapy for HIV-infected children include:

- Reducing HIV-related mortality and morbidity
- Restoring and preserving immune function
- Maximally and durably suppressing viral replication
- Minimizing drug-related toxicity
- Maintaining normal physical growth and neurocognitive development
- Improving quality of life

Strategies to achieve these goals require complex balancing of sometimes competing considerations.

Use and selection of combination antiretroviral therapy: At present, the treatment of choice for HIV-infected children is at least 3 drugs, which include at least 2 classes of antiretroviral drugs. The Working Group has recommended several preferred and alternative regimens (see What Drugs to Start: Initial Combination Therapy for Antiretroviral-Naïve Children in the original guideline document). The most appropriate regimen for an individual child depends on multiple factors, including age of the child and availability of appropriate drug formulations; the potency, complexity, and toxicity of the regimen; the child and caregiver's ability to adhere to the regimen; the child's home situation; and the child's antiretroviral treatment history.

Drug sequencing and preservation of future treatment options: The choice of antiretroviral treatment regimens should include consideration of future treatment options, such as the presence of or potential for drug resistance. Multiple changes in antiretroviral drug regimens can rapidly exhaust treatment options, and should be avoided unless required (e.g., severe toxicity or intolerance or significant clinical, immunologic, or virologic progression). Appropriate sequencing of drugs for use in initial and second-line therapy can preserve future treatment options and is another strategy to maximize long-term benefit from therapy. Currently, recommendations for initial therapy are to use 2 classes of drugs—2 nucleoside

analogue reverse transcriptase inhibitors (NRTIs) combined with either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or protease inhibitor (PI)—thereby sparing 3 classes of drugs for later use.

Maximizing adherence: As discussed in the Adherence to Antiretroviral Therapy in HIV-Infected Children and Adolescents section of the original guideline document, lack of adherence to prescribed regimens can lead to subtherapeutic levels of antiretroviral medications, which enhances the risk of the development of drug resistance and likelihood of virologic failure. Participation by the caregivers and child in the decision-making process is crucial. Issues related to adherence to therapy should be fully assessed, discussed, and addressed with the child's caregiver and the child (when age-appropriate) before the decision to initiate therapy is made. Potential problems should be identified and resolved prior to starting therapy, even if this delays initiation of therapy. Additionally, frequent follow-up is important to provide assessment of virologic response to therapy, drug intolerance, viral resistance, and adherence. Finally, in patients who experience virologic failure, it is critical to fully assess adherence before making changes to the antiretroviral regimen.

When to Initiate Therapy in Antiretroviral-Naïve Children (see Table 2 in the original guideline document)

The choice of whether to start therapy early, while an individual is still asymptomatic, versus delaying therapy until clinical or immunologic deterioration occurs, continues to generate considerable controversy among HIV experts. Some experts favor starting aggressive therapy in the early stages of HIV infection in the hope that early antiretroviral intervention will control viral replication prior to the onset of rapid genetic mutation and evolution into multiple quasispecies. This could result in a lower viral set point, fewer mutant viral strains, and potentially less drug resistance. Early therapy would slow immune system destruction and preserve immune function, preventing clinical disease progression. On the other hand, delaying therapy until later in the course of HIV infection, when clinical or immunologic symptoms appear, may result in reduced evolution of drug-resistant virus due to a lack of drug selection pressure, greater adherence to the therapeutic regimen when the patient is symptomatic rather than asymptomatic, and reduced or delayed adverse effects of antiretroviral therapy.

Recommendations for when to initiate therapy have been more aggressive in children than adults because HIV infection is primarily transmitted from mother to child, thereby allowing identification of the timing of infection in children; HIV disease progression in children is more rapid than in adults; and laboratory parameters are less predictive of risk of disease progression in children, particularly for young infants. As discussed in the Laboratory Monitoring of Pediatric HIV Infection section in the original guideline document, CD4 count and HIV RNA values vary considerably by age in children, and both markers are poorly predictive of disease progression and mortality in children younger than 12 months. Hence, recommendations for when to start therapy differ by age of the child. As discussed earlier, in the HIV Pediatric Prognostic Markers Collaborative Study (HPPMCS) meta-analysis, CD4 percentage and HIV RNA levels were both independently predictive of the risk of clinical progression or death, although CD4 percentage was a stronger predictor of risk than HIV RNA levels. Based on data showing that surrogate-marker based risk of progression varies considerably by

age but that CD4 count-associated risk of progression in children age 5 years or older is similar to young adults, the Working Group has moved to recommendations for 3 age bands for initiation of treatment: infants under age 12 months, children age 1 to <5 years, and children and adolescents age ≥5 years.

Antiretroviral-Naïve HIV-Infected Infants Under Age 12 Months

Working Group Recommendations

- Initiation of antiretroviral therapy is *recommended* for infants aged <12 months, regardless of clinical status, CD4 percentage, or viral load.
- Issues associated with adherence must be fully assessed and discussed with the HIV-infected infant's caregivers before therapy is initiated.

While there is agreement among pediatric HIV experts that infected infants with clinical symptoms of HIV disease or with evidence of immune compromise should be treated, there remains controversy regarding treatment of asymptomatic infants with normal immunologic status. However, recent data from a South African clinical trial (Children with HIV Early Antiretroviral Therapy [CHER] study) of initiation of highly active antiretroviral therapy (HAART) in asymptomatic perinatally-infected children with normal CD4 percentage (CD4 >25%) prior to age 12 weeks compared to waiting to start HAART until the child meets clinical or immune criteria, demonstrated a 75% reduction in early mortality. Most of the deaths in the children in the delayed arm occurred in the first 6 months after study entry. Because the risk of rapid progression is so high in young infants and based on the data from the CHER study, the Working Group recommends initiation of therapy for all infants age <12 months regardless of clinical status, CD4 percentage or viral load (see Table 2 in the original guideline document). It is critical that issues associated with adherence are fully assessed and discussed with the HIV-infected infant's caregivers and addressed before therapy is initiated.

Refer to the original guideline document for a detailed discussion.

Antiretroviral-Naïve HIV-Infected Children Age 1 Year or Older

Working Group Recommendations

- Initiation of antiretroviral therapy is *recommended* for children age ≥1 year with AIDS or significant symptoms (clinical category C or most clinical category B conditions; see Table 1 of the original guideline document), regardless of CD4 percentage/count or plasma HIV RNA level.
- Initiation of antiretroviral therapy is also *recommended* for children age ≥1 year who have met the age-related CD4 threshold for initiating treatment (CD4 <25% for children aged 1 to <5 years and <350 cells/mm^3 for children ≥5 years), regardless of symptoms or plasma HIV RNA level.
- Initiation of antiretroviral therapy should be *considered* for children age ≥1 year who are asymptomatic or have mild symptoms (clinical category N and A or the following clinical category B conditions: single episode of serious bacterial infection or lymphoid interstitial pneumonitis) *and* have CD4 ≥25%

for children aged 1 to <5 years or ≥350 cells/mm^3 for children ≥5 years *and* have plasma HIV RNA ≥100,000 copies/mL.
- Initiation of antiretroviral therapy may be *deferred* for children age ≥1 year who are asymptomatic or have mild symptoms *and* who have CD4 ≥25% for children aged 1 to <5 years and ≥350 cell/mm^3 for children ≥5 years *and* have plasma HIV RNA <100,000 copies/mL.

Because the risk of disease progression slows in children age ≥1 year, the option of deferring treatment can be considered for older children. It is clear that children with clinical AIDS or significant symptoms (clinical category C or B; see Table 1 in the original guideline document) are at high risk of disease progression and death; treatment is recommended by the Working Group for all such children, regardless of immunologic or virologic status. However, children age ≥1 year with mild clinical symptoms (clinical category A) or who are asymptomatic (clinical category N) are at lower risk of disease progression than those with more severe clinical symptoms. It should also be noted that some clinical category B conditions—a single episode of serious bacterial infection or lymphoid interstitial pneumonitis—are less prognostic of the risk of disease progression, and consideration of CD4 count and viral load may be useful in determining the need for therapy in such children.

When therapy is deferred, the health care provider should closely monitor virologic, immunologic, and clinical status (see the Laboratory Monitoring of Pediatric HIV Infection section in the original guideline document). Factors to be considered in deciding when to initiate therapy in such children include:

- Increasing HIV RNA levels (e.g., HIV RNA levels approaching 100,000 copies/mL)
- Rapidly declining CD4 count or percentage to values approaching the age-related threshold for consideration of therapy
- Development of clinical symptoms
- The ability of caregiver and child to adhere to the prescribed regimen

What Drugs to Start: Initial Combination Therapy for Antiretroviral-Naïve Children (see Tables 3 through 9 in the original guideline document)

Working Group Recommendations

- Combination therapy with at least 3 drugs, including either a protease inhibitor or non-nucleoside reverse transcriptase inhibitor plus a dual nucleoside analogue reverse transcriptase inhibitor backbone, is recommended for initial treatment of HIV-infected children.
- The goal of therapy in treatment-naïve children is to reduce HIV RNA levels to below the level of detection (if possible, as determined using ultrasensitive assays) and to preserve immune function for as long as possible.
- Infants who are identified as HIV-infected during the first 6 weeks of life while receiving zidovudine chemoprophylaxis should have zidovudine discontinued and initiate treatment with combination therapy with at least 3 drugs (with drug choice based on results from antiretroviral drug resistance testing and

treatment only initiated following assessment and counseling of the caregivers regarding adherence to therapy).
- Antiretroviral drug resistance testing is recommended prior to initiation of therapy in all treatment-naïve children.

Recommended Regimens for Initial Therapy of Antiretroviral-Naïve Children *(see Tables 3 and 4 in the original guideline document)*

NNRTI-Based Regimens (1 NNRTI + 2 NRTI backbone)

Working Group Recommendations

- Preferred NNRTI:
  - Efavirenz in combination with 2 NRTIs for children age ≥3 years
  - Nevirapine in combination with 2 NRTIs for children age <3 years or who require a liquid formulation
- Alternative NNRTI:
  - Nevirapine in combination with 2 NRTIs (for children age ≥3 years)

The Working Group does not recommend the following NNRTIs as initial therapy in children:

- Etravirine, due to lack of pediatric formulation, lack of pediatric pharmacokinetic data, lack of efficacy or safety data in children, and lack of data in antiretroviral naïve patients

Nevirapine and efavirenz both have an approved pediatric indication. Nevirapine is available in a liquid formulation, while efavirenz is not, although a liquid formulation of efavirenz is under study. Advantages and disadvantages of different NNRTI drugs are delineated in Table 6 in the original guideline document. Use of NNRTIs as initial therapy preserves the PI class for future use, and less dyslipidemia and fat maldistribution have been reported with the NNRTI class than with the PI class. Additionally, there is a lower pill burden with these agents when compared to PI-based regimens for children taking solid formulations. The major disadvantage of the current NNRTI drugs is that a single viral mutation can confer drug resistance, and cross-resistance develops between nevirapine and efavirenz. Rare but serious and potentially life-threatening skin and hepatic toxicity can occur with all drugs in this class, but is most frequent with nevirapine, at least in HIV-infected adults.

Efavirenz, in combination with 2 NRTIs, is the preferred NNRTI for initial therapy of children age ≥3 years based on clinical trial experience in children and because higher rates of toxicity have been observed with nevirapine in clinical trials in adults. Results of studies comparing virologic response to nevirapine- versus efavirenz-based regimens in adults are conflicting, and no comparative studies have been done in children. Because nevirapine therapy is associated with the rare occurrence of significant hypersensitivity reactions, including Stevens-Johnson syndrome, and rare but potentially life-threatening hepatitis, nevirapine

is recommended as an alternative NNRTI for initial treatment of antiretroviral-naïve children age ≥3 years. Nevirapine is the preferred NNRTI for initial therapy of children age <3 years or for children who require a liquid formulation.

PI-Based Regimens (1 or 2 PIs + 2 NRTI backbone)

Working Group Recommendations

- Preferred PI
  - Lopinavir/ritonavir in combination with 2 NRTIs
- Alternative PI (listed alphabetically)
  - Atazanavir in combination with low dose ritonavir and 2 NRTIs (for children age ≥6 years)
  - Fosamprenavir in combination low dose ritonavir and 2 NRTIs (for children age ≥6 years)
  - Nelfinavir and 2 NRTIs (for children age ≥2 years)
- Use in special circumstances:
  - Atazanavir unboosted (for treatment-naïve adolescents age ≥13 years and >39 kg who are unable to tolerate ritonavir) in combination with 2 NRTIs (must be boosted with ritonavir if used with tenofovir)
  - Fosamprenavir unboosted (for children age ≥2 years) in combination with 2 NRTIs

The Working Group does not recommend the following PIs as initial therapy in children because of insufficient data, data related to toxicity or potency, or inconvenient dosing:

- Tipranivir, darunavir, saquinavir, indinavir and other PIs not in the list above
- Dual (full dose) PIs
- Full dose ritonavir or use of ritonavir as the sole PI
- Unboosted atazanavir-containing regimens in children age <13 years and/or <39 kg

Nine PIs are currently approved for use, 7 of which are approved for use in children and have pediatric drug formulations. Advantages and disadvantages of different PIs are delineated in Table 7 in the original guideline document. Advantages of PI-based regimens include excellent virologic potency, high barrier for development of drug resistance (requires multiple mutations), and sparing of the NNRTI drug class. However, the drugs have potential for multiple drug interactions due to metabolism via hepatic enzymes, and may be associated with metabolic complications such as dyslipidemia, fat maldistribution, and insulin resistance. Factors to be considered in selecting a PI-based regimen for treatment-naïve children include virologic potency, dosing frequency, pill burden, food or fluid requirements, availability of palatable pediatric formulations, drug interaction profile, toxicity profile (particularly related to metabolic complications), and availability of data in children (see Table 7 in the original guideline document for advantages and disadvantages and Supplement I: Pediatric Antiretroviral Drug Information in the original guideline document for detailed pediatric information on each drug).

Ritonavir acts as a potent inhibitor of the cytochrome P450 3A4 (CYP3A4) isoenzyme, thereby inhibiting the metabolism of other PIs, and has been used in low doses combined with another PI as a "pharmacokinetic booster," increasing drug exposure by prolonging the second drug's half-life. Boosted PI-based regimens are commonly used in treatment of adults, but adequate pediatric data are only available for coformulated lopinavir/ritonavir in children over age 6 weeks and atazanavir ,fosamprenavir, and darunavir with low-dose ritonavir in children age >6 years. The appropriate dosing of ritonavir-boosted PI regimens for other combinations is not known in children, and additional pharmacokinetic studies are necessary before more definitive dosing recommendations can be made and before such regimens can be recommended for initial therapy of treatment-naïve children. Additionally, the use of low-dose ritonavir increases the potential for hyperlipidemia and drug-drug interactions.

The Working Group recommends coformulated lopinavir/ritonavir as the preferred PI for the treatment-naïve child based on virologic potency in adult and pediatric studies, high barrier to development of drug resistance, excellent toxicity profile in adults and children, and availability of appropriate dosing information for children. However, data comparing the efficacy of lopinavir/ritonavir to other PIs are limited in adults and not available in children. Three PIs can be considered as alternative PIs for use in children: atazanavir in combination with low dose ritonavir for children age >6 years, fosamprenavir in combination with low dose ritonavir for children age >6 years, or nelfinavir for children age >2 years. Other PIs that can be considered in special circumstances when preferred and alternative drugs are not available or are not tolerated include fosamprenavir alone in children age >2 years, atazanavir alone in adolescents age >13 years and >39 kg, or for older adolescents, saquinavir in combination with low dose ritonavir as discussed above. While good virologic and immunologic responses have been observed with indinavir-based regimens in adults, there is no liquid formulation and there has been a high rate of hematuria, sterile leukocyturia, and nephrolithiasis reported in pediatric patients with this drug. The incidence of hematuria and nephrolithiasis with indinavir therapy may be higher in children than adults. Therefore, indinavir alone or with ritonavir boosting is not recommended as initial therapy. Additionally, newer PIs such as tipranavir and darunavir are not recommended for initial therapy at the present time due to limited data on use in treatment-naïve children, but may be considered for use in children with treatment failure.

Refer to the original guideline document for a detailed discussion.

Triple NRTI Regimens

Working Group Recommendations

- Use in special circumstances:
  - A 3 NRTI-based regimen consisting of zidovudine + lamivudine + abacavir should only be used in special circumstances when a preferred or alternative NNRTI-based or PI-based regimen cannot be used as first-line therapy in treatment-naïve children (e.g., due to significant drug interactions or adherence concerns).

The Working Group does not recommend the following triple NRTI regimens as initial

therapy in children due to inferior virologic potency:

- Tenofovir + abacavir + lamivudine
- Tenofovir + didanosine + lamivudine

Triple NRTI regimens are attractive for use in HIV-infected pediatric patients as initial therapy because of the ease of administration, availability of palatable liquid formulations, demonstrated tolerance, and avoidance of many drug interactions. Because these triple NRTI regimens can be administered twice a day in children (adolescents who can receive adult doses can consider the triple combination of zidovudine/lamivudine/abacavir in a fixed-dose single tablet formulation [Trizivir]), they may also facilitate adherence. Data on the efficacy of triple NRTI regimens for treatment of antiretroviral-naïve children are limited; in small observational studies, response rates of 47% to 50% have been reported. In adult trials, these regimens have shown less potent virologic activity when compared to NNRTI- or PI-based regimens. Based on the results of these clinical trials and the potentially life-threatening hypersensitivity syndrome associated with abacavir use, the Working Group recommends that a 3 NRTI-based regimen consisting of zidovudine + lamivudine + abacavir should only be used in special circumstances when a preferred or alternative NNRTI-based or PI-based regimen cannot be used as first-line therapy in treatment-naïve children (e.g., due to significant drug interactions or concerns related to adherence).

Selection of Dual NRTI Backbone as Part of Initial Combination Therapy

Working Group Recommendations

- Preferred 2 NRTI backbone combinations:
  - Abacavir + (lamivudine *or* emtricitabine)
    - HLA B*5701 genetic testing should be considered for HIV-infected children prior to initiating abacavir-based therapy, and abacavir should not be given to a child who tests positive for HLA B*5701
  - Didanosine + emtricitabine
  - Zidovudine + (lamivudine *or* emtricitabine)
  - For post-pubertal or Tanner Stage 4 adolescents: tenofovir + (lamivudine *or* emtricitabine)
- Alternative 2 NRTI backbone combinations:
  - Zidovudine + (abacavir *or* didanosine)
- Use in special circumstances:
  - Stavudine + (lamivudine *or* emtricitabine)

The Working Group does not recommend the following dual NRTI backbones for use in children:

- Tenofovir-containing dual NRTI combinations in children in Tanner Stages 1 to 3 due to lack of pediatric dosing data and formulation and concerns related to bone toxicity
- Zidovudine + stavudine due to virologic antagonism

- Lamivudine + emtricitabine due to similar resistance pattern and no additive benefit
- Stavudine + didanosine due to toxicity (although not recommended for initial therapy, may be considered for use in antiretroviral-experienced children who require a change in therapy)

Currently, 6 NRTIs (zidovudine, didanosine, lamivudine, stavudine, abacavir, and emtricitabine) are FDA-approved for use in children less than 13 years of age. Dual NRTI combinations form the "backbone" of HAART regimens for both adults and children. Dual NRTI combinations that have been studied in children include zidovudine in combination with abacavir, didanosine, or lamivudine; abacavir in combination with lamivudine, stavudine, or didanosine; and emtricitabine in combination with stavudine or didanosine. Advantages and disadvantages of different dual NRTI backbone options are delineated in Table 5 in the original guideline document.

The preferred dual NRTI combinations for initial therapy in children consist of a primary NRTI (abacavir, didanosine, or zidovudine) combined with either lamivudine or emtricitabine. The most extensive experience in children is with zidovudine in combination with lamivudine. Selection of the lamivudine- (or emtricitabine-) associated M184V mutation has been associated with increased susceptibility to zidovudine or tenofovir. This combination has extensive data on safety in children and is generally well tolerated. The major toxicities are bone marrow suppression, manifested as macrocytic anemia and neutropenia. Minor toxicities include gastrointestinal toxicity and fatigue.

Both lamivudine and emtricitabine are well tolerated with few side effects. While there is less experience in children with emtricitabine than lamivudine, it is similar to lamivudine, and the Working Group felt it could be substituted for lamivudine as one component of a preferred dual regimen (i.e., emtricitabine in combination with abacavir, didanosine, or zidovudine). The advantages of emtricitabine are once daily administration, ability to be coadministered with didanosine, and its recent availability as an oral solution. Both lamivudine and emtricitabine select for the M184V resistance mutation, which is associated with high-level cross resistance between both drugs, a modest decrease in susceptibility to abacavir and didanosine, and improved susceptibility to zidovudine, stavudine, and tenofovir.

Abacavir in combination with lamivudine has been shown to be as or possibly more potent than zidovudine in combination with lamivudine in both children and adults, but has the potential for abacavir-associated life-threatening hypersensitivity reactions in a small proportion of patients. Abacavir hypersensitivity is more common in individuals with certain HLA genotypes, particularly HLA B*5701 (see Supplement I: Pediatric Antiretroviral Drug Information in the original guideline document); however the prevalence of HLA B*5701 is much lower in African American and Hispanic than Caucasian individuals in the United States (2% to 2.5% compared to 8%); the majority of HIV-infected children in the United States are of minority race/ethnicity. Pre-treatment screening for HLA B*5701 prior to initiation of abacavir treatment resulted in a significant reduction in the rate of abacavir hypersensitivity reaction

in a study in HIV-infected adults. Genetic screening for HLA B*5701 should be considered for HIV-infected children prior to initiating abacavir-based therapy. If testing is done, abacavir should not be given to children who test positive for HLA B*5701.

Didanosine in combination with emtricitabine is also a preferred dual NRTI combination because of the potential for once daily dosing. In a study in 37 treatment-naïve children aged 3 to 21 years, long-term virologic suppression was achieved with a once daily regimen of didanosine, emtricitabine, and efavirenz; 72% of subjects maintained HIV RNA suppression to <50 copies/mL through 96 weeks of therapy. Prescribing information for didanosine recommends administration on an empty stomach. However, this is impractical for infants who feed frequently, and may decrease medication compliance in older children by increasing regimen complexity. A comparison of didanosine given with or without food in children found that systemic exposure was similar, but with slower and more prolonged absorption with food. To improve compliance, some practitioners recommend administration without regard to timing of meals for young children. However, there are inadequate data to allow a strong recommendation at this time, and it is preferred that didanosine be administered under fasting conditions when possible.

Tenofovir has been studied in HIV-infected children in combination with other NRTIs and as an investigational oral sprinkle/granule formulation. Tenofovir in combination with lamivudine or emtricitabine is a preferred dual NRTI combination for use in adolescents in Tanner Stage 4 or who are post-puberty. The fixed-dose combinations of tenofovir + emtricitabine and tenofovir + emtricitabine + efavirenz are both administered as one pill once daily and may be particularly useful to improve adherence in older adolescents. In studies in adults, tenofovir when used with lamivudine or emtricitabine in combination with efavirenz had potent viral suppression for up to 3 years and was superior to zidovudine/lamivudine in viral efficacy. A tenofovir-based dual NRTI combination has not been studied head-to-head with another dual NRTI backbone in a PI-based regimen but 48-week virologic efficacy of tenofovir + emtricitabine in combination with lopinavir/ritonavir was similar to that seen in trials with other dual NRTI backbones in treatment-naïve adults. However, decreases in bone mineral density have been shown in both adults and children taking tenofovir for 48 weeks in some, although not all, studies. At this time there are insufficient data to recommend use of this drug for initial therapy in infected children in Tanner Stage 1–3, in whom the risk of bone toxicity may be greatest (see Supplement I: Pediatric Antiretroviral Drug Information in the original guideline document for more detailed pediatric information). Renal toxicity has been reported in children as well as adults receiving tenofovir; in one single-center study, the rate of beta-2-microglobulinemia was higher in children receiving tenofovir than children receiving other antiretroviral agents (12/44 compared to 2/48, respectively), although creatinine clearance did not differ between groups. Because of potential bone toxicity and renal toxicity, the drug may have greater utility for treatment of children in whom other antiretroviral drugs have failed than for initial therapy of treatment-naïve children. There are numerous drug-drug interactions with tenofovir and other antiretroviral drugs, including didanosine, lopinavir/ritonavir, atazanavir, and tipranavir, complicating appropriate dosing of this drug.

Alternative dual NRTI combinations include zidovudine in combination with abacavir or didanosine. There is considerable experience with use of these dual NRTI regimens in children. However, zidovudine + abacavir (as well as zidovudine + lamivudine) had lower rates of viral suppression and more toxicity leading to switching than did abacavir + lamivudine in one European pediatric study.

The dual NRTI combination of stavudine in combination with lamivudine or emtricitabine is recommended for use in special circumstances because stavudine is associated with a higher risk of lipoatrophy and hyperlactatemia than other NRTI drugs. For example, for children with anemia in whom there are concerns related to abacavir hypersensitivity and who are too young to receive tenofovir, stavudine may be preferred to zidovudine due to its lesser hematologic toxicity.

Certain dual NRTI drug combinations are not recommended. These include zidovudine + stavudine due to pharmacologic interactions that can result in potential virologic antagonism. The drug structure of emtricitabine is similar to lamivudine and the same single resistance mutation confers cross-resistance, so these drugs should not be used in combination. The dual NRTI combination of stavudine + didanosine is also not recommended for use as initial therapy. In small pediatric studies, stavudine + didanosine demonstrated virologic efficacy and was well tolerated. However, in studies in adults, stavudine + didanosine-based combination regimens were associated with greater rates of neurotoxicity, pancreatitis, hyperlactatemia and lactic acidosis, and lipodystrophy than therapies based on zidovudine + lamivudine; additionally, cases of fatal and non-fatal lactic acidosis with pancreatitis/hepatic steatosis have been reported in women receiving this combination during pregnancy.

Insufficient Data for Recommendation for Initial Therapy for Children

Working Group Recommendations

Because of insufficient data for use as initial therapy, the following regimens should not be offered to children for initial therapy:

- Low-dose ritonavir-boosted PI regimens, with exceptions of lopinavir/ritonavir (all ages), atazanavir/ritonavir in children age ≥6 years, and fosamprenavir/ritonavir in children age ≥6 years
- Dual (full dose) PI regimens
- Unboosted atazanavir-containing regimens in children age <13 years and/or <39 kg
- NRTI plus NNRTI plus PI
- Tenofovir-containing regimens in children in Tanner Stages 1 to 3
- Tipranavir- or darunavir-containing regimens
- Maraviroc-containing regimens
- Raltegravir-containing regimens
- Etravirine-containing regimens
- Enfuvirtide (T-20)-containing regimens

What Not to Use: Antiretroviral Drug Regimens That Should Not Be Offered at Any Time (see Table 4 in the original guideline document)

Working Group Recommendations

The following regimens should not be offered to children at any time:

- Monotherapy
- Two NRTIs alone
- Certain 2 NRTI combinations as part of HAART regimen
- Two NRTIs + unboosted saquinavir
- Atazanavir + indinavir
- Tenofovir + didanosine + (lamivudine *or* emtricitabine)
- Tenofovir + abacavir + (lamivudine *or* emtricitabine)

Monitoring of Children on Antiretroviral Therapy

Working Group Recommendations

- Children who start a new antiretroviral regimen should be evaluated in person or by a phone call within 1 to 2 weeks of starting medication to screen for clinical side effects and to assure that they are taking medication properly.
- Children should be seen within 4 to 8 weeks to assess for possible side effects and to evaluate initial response to therapy. More frequent evaluation may be needed following initiation or change in therapy to support adherence to the regimen.
- Subsequently, children should have a monitoring visit at least every 3 to 4 months to assess both efficacy and potential toxicity of their antiretroviral regimens.

Children who start a new antiretroviral regimen or who change to a new regimen should be followed to assess effectiveness, adherence, tolerability, and side effects of the regimen. Frequent patient visits and intensive follow-up during the initial months after a new antiretroviral regimen is started are necessary to support and educate the family. The first few weeks of antiretroviral therapy can be particularly difficult for children and their caregivers. They must adjust their schedules to allow for consistent and routine administration of medication doses. Children may also experience side effects of medications, and the child and caregiver need assistance in determining whether the effects are temporary and can be tolerated or whether they are more serious or long-term and necessitate a visit to the clinician. Thus, it is prudent for the clinician to assess the child within 1 to 2 weeks of initiating therapy, either in person or with a phone call, to assure proper administration of medications and to evaluate clinical concerns. Many clinicians will plan additional contact (in person or by telephone) with the child and caregivers during the first few weeks of therapy to support adherence.

Baseline laboratory assessments should be done prior to initiation of therapy; these include CD4 count/percentage and HIV RNA level; complete blood count and differential; serum chemistries (including electrolytes, blood urea nitrogen [BUN], creatinine, glucose, hepatic transaminases, calcium, and phosphorus); pancreatic enzyme evaluations (amylase, lipase) if therapy is being initiated with a drug with

potential pancreatic toxicity, such as didanosine; and serum lipid evaluation (cholesterol, triglycerides). The child should be seen within 4 to 8 weeks after initiating or changing therapy to obtain a clinical history, with a focus on potential adverse effects and to assess adherence to medications; perform a physical examination; evaluate efficacy of therapy (measurement of CD4 count/percentage and HIV RNA levels); and to obtain a laboratory evaluation for toxicity. More frequent evaluation may be needed following a change in therapy to support adherence to the regimen. At a minimum, laboratory assessments should include a complete blood count and differential, serum chemistries, and assessment of renal and hepatic function. Assessment of initial virologic response to therapy is important, as an initial decrease in HIV viral load in response to antiretroviral treatment should be observed after 4 to 8 weeks of therapy.

Subsequently, children taking antiretroviral medication should have assessments of adherence, toxicity, and efficacy at least every 3 to 4 months. Table 10 in the original guideline document provides one proposed monitoring schema, which will require adjustment based on the specific therapy the child is receiving. Assessments should include basic hematology, chemistry, CD4 count/percentage, and HIV viral load. Monitoring of drug toxicities should be tailored to the particular medications the child is taking; for example, periodic monitoring of pancreatic enzymes may be desirable in children receiving didanosine, or of serum glucose and lipids in patients receiving PIs. Children who develop symptoms of toxicity should have appropriate laboratory evaluations (e.g., evaluation of serum lactate in a child receiving NRTI drugs who develops symptoms suspicious for lactic acidosis) performed more frequently until the toxicity resolves. For further details of adverse effects associated with particular antiretroviral medications, please see Supplement III: Adverse Drug Effects in the original guideline document.

Specific Issues in Antiretroviral Therapy for HIV-Infected Adolescents

Working Group Recommendations

- Antiretroviral therapy regimens must be individually tailored to the adolescent, as those with perinatal exposure generally have a very different clinical course and treatment history than those who acquired HIV during adolescence.
- Appropriate dosing of antiretroviral medications for adolescents is complex, not always predictable, and dependent upon multiple factors, including Tanner staging of puberty, body mass and chronologic age.
- Effective and appropriate contraceptive methods should be selected to reduce the likelihood of unintended pregnancy. Providers should be aware of potential interactions between antiretroviral drugs and hormonal contraceptives, which could lower contraceptive efficacy.
- Efavirenz should be avoided for the adolescent girl who desires to become pregnant or who does not use effective and consistent contraception. Efavirenz also should be avoided throughout the first trimester of pregnancy.
- Pediatric and adolescent care providers should work with older adolescent patients to prepare them for transition into adult care settings.

Working Group Recommendations

- Strategies to maximize adherence should be discussed prior to initiation of antiretroviral therapy and again at the time of changing regimens.
- Adherence to therapy must be stressed at each visit, along with continued exploration of strategies to maintain and/or improve adherence.
- Multiple methods of determining adherence to antiretroviral therapy should be used simultaneously (e.g., quantitative self-report, pharmacy refill checks, pill counts).
- A non-judgmental attitude and trusting relationship will foster open communication and ease assessment of adherence.

Adherence Assessment and Monitoring

The process of adherence preparation and assessment should begin before therapy is initiated or changed, and a routine adherence assessment should be incorporated into every clinic visit. A comprehensive assessment should be instituted for all children in whom antiretroviral treatment initiation or change is considered. Evaluations should include nursing, social, and behavioral assessments of factors that may affect adherence by the child and family and can be used to identify individual needs for intervention. Adherence preparation should focus on establishing a dialogue and a partnership in medication management. Specific, open-ended questions should be used to elicit information about past experience as well as concerns and expectations about treatment. When assessing readiness and preparing to begin treatment, it is important to obtain explicit agreement with the treatment plan, including strategies to support adherence.

Adherence is difficult to assess accurately; different methods of assessment have been shown to yield different results, and each approach has limitations. Both caregivers and health care providers often overestimate adherence. Regular monitoring is key to early identification of problems and can reinforce the importance of taking medications as prescribed.

Use of multiple methods to assess adherence is recommended. Viral load response to a new regimen is often the most accurate indication of adherence, but it may be a less valuable measure in children with long treatment histories and multi-drug-resistant virus. Other measures include quantitative self-report of missed doses by caregivers and children or adolescents (focusing on recent missed doses during a 3-day or 1-week period), descriptions of the medication regimens, and reports of barriers to administration of medications. Targeted questions about stress, pill burden, and daily routine are recommended. Pharmacy refill checks and pill counts can identify adherence problems not evident from self-reports. Electronic monitoring devices, such as Medication Event Monitoring Systems (MEMS) caps, which record opening of medication bottles on a computer chip in the cap, have been shown to be useful tools to measure adherence in some settings. Home visits can play an important role in assessing adherence,

and in some cases, suspected nonadherence is confirmed only when dramatic clinical responses to antiretroviral therapy occur during hospitalizations or in other supervised settings. Preliminary studies suggest that monitoring plasma concentrations of PIs, or therapeutic drug monitoring, may be a useful method to identify nonadherence.

It is important for clinicians to recognize that nonadherence is a common problem and that it can be difficult for patients to share information about missed doses or difficulties adhering to treatment. Furthermore, adherence can change over time. An adolescent who was able to strictly adhere to treatment upon initiation of a regimen may not be able to maintain complete adherence over time. A non-judgmental attitude and trusting relationship fosters open communication and facilitates assessment. It is often helpful to ask both older children and caregivers about missed doses and problems. There can be significant discrepancies between parent and child reports. Therefore, clinical judgment is required to best interpret adherence information obtained from multiple sources.

See the original guideline document for strategies to improve and support adherence, including regimen-related strategies, child/family-related strategies, and health care provider-related strategies.

Management of Medication Toxicity or Intolerance

Working Group Recommendations

- If a child has severe or life-threatening toxicity, all components of the drug regimen should be stopped immediately. Once the symptoms of toxicity have resolved, antiretroviral therapy should be resumed with substitution of another antiretroviral drug for the responsible drug.
- Children with moderate medication toxicity should continue on antiretroviral therapy when possible while an assessment is done to identify and substitute for the offending agent.
- Children with mild toxicity can be treated symptomatically, and do not require drug discontinuation or change in drug therapy.
- When changing therapy because of toxicity or intolerance to a specific drug, changing a single drug in a multi-drug regimen is permissible; if possible, an agent with a different toxicity and side effect profile should be chosen.
- The toxicity and the medication thought to be responsible for it should be documented in the medical record and the caregiver and patient made aware of the drug-related toxicity to assist in making future medication choices if care is transferred.
- Dose reduction is not a recommended option in the setting of antiretroviral toxicity except in the instance when therapeutic drug monitoring has been performed and indicated a drug concentration above the normal therapeutic range.

Management strategies for drug intolerance include:

- Symptomatic treatment of mild to moderate transient side effects

- Change from one drug to another drug to which the patient's virus is sensitive within the same drug class, if necessary (e.g., change to stavudine for zidovudine-related anemia or to nevirapine for efavirenz-related central nervous system symptoms)
- Change drug classes, if necessary (e.g., from PI to an NNRTI or vice versa) and if the patient's virus is sensitive to a drug in that class
- Dose reduction only when drug levels have been determined to be excessive

Antiretroviral Treatment Failure in Infants, Children, and Adolescents

Working Group Recommendations

- The goal of therapy following treatment failure is to achieve and maintain virologic suppression, as measured by a plasma viral load below the limits of detection using the most sensitive assay.
- When complete virologic suppression cannot be achieved, the goals of therapy are to preserve or restore immunologic function (as measured by CD4 lymphocyte values), prevent clinical disease progression, and preserve future antiretroviral options.
- Not all instances of treatment failure require an immediate change in therapy; careful assessment, especially of adherence, is required to evaluate the etiology of the treatment failure and determine an appropriate management strategy.
- Children who experience treatment failure should be managed in collaboration with a pediatric HIV specialist.

Assessment of Patients with Antiretroviral Treatment Failure

Working Group Recommendations

- Assess adherence to therapy, barriers and interventions to improve adherence, as inadequate adherence is the most common cause of antiretroviral treatment failure.
- Assess medication intolerance.
- Assess issues related to pharmacokinetics. Developmental and individual differences in drug absorption, distribution, metabolism, and elimination can cause inadequate antiretroviral drug exposure that results in antiretroviral treatment failure.
- Perform antiretroviral drug resistance testing when virologic failure occurs and prior to changing to a new regimen.
- Perform assessment in collaboration with a pediatric HIV specialist.

Each patient with an incomplete response to therapy should be assessed to determine the cause of treatment failure, as the approach to management and subsequent treatment may differ depending on the etiology of the problem. In most instances, treatment failure is multifactorial. The assessment of a child with suspicion of treatment failure should include evaluation of adherence to therapy, medication intolerance, issues related to pharmacokinetics that could result in low

drug levels or elevated, potentially toxic levels, and evaluation of suspected drug resistance. The main challenge to long-term maintenance of undetectable plasma viral load in adults and children is incomplete adherence to medication regimens, with the subsequent emergence of viral mutations conferring partial or complete resistance to one or more of the components of the antiretroviral regimen.

The table below outlines a comprehensive approach to evaluating causes of treatment failure in children with particular attention to adherence. An extensive history should focus on the details of drug administration as well as changes in the social and psychological circumstances of the family likely to impact on the child's ability to adhere to their regimen. In some situations, it may be necessary to directly observe drug-taking behaviors either in the clinic, at home, or within the hospital as history alone may not fully identify the barriers to complete adherence.

Table: Assessment of Antiretroviral Treatment Failure

Assessment	Method	Intervention

Adherence	1. Interview child and caretaker
	• 24 hour or 7 day recall
	• Description of:
	  • *WHO* gives medication
	  • *WHAT* is given (names, doses)
	  • *WHERE* medications are kept, administered
	  • *WHEN* they are taken/given
	• Open ended discussion of experiences taking/giving medications and barriers/challenges
	
	2. Review pharmacy records
	• Assess timeliness of refills
		• Identify or re-engage family members to support/supervise adherence.
		• Establish fixed daily times and routines for medication administration.
		• Avoid confusion with drug names by explaining that drug therapies have generic names, trade names, and many agents are coformulated under a third or fourth name.
		• Explore opportunities for facility or home-based directly observed therapy.

	3. Observe medication administration	• Simplify medication regimen if

Assessment	Method	Intervention
	• Observe dosing/administration in clinic • Home based observation by visiting health professional • Hospital admission for trial of therapy • Observe administration/tolerance monitor treatment response	feasible. • Substitute new agents if single ARV is poorly tolerated. • Consider gastric tube placement to facilitate adherence. • Directly observed therapy (DOT) • Utilization of tools to simplify administration (pill boxes, reminders including alarms, integrated medication packaging for AM or PM dosing, others) • Relaxation techniques

	4. Psychosocial assessment
	• Comprehensive family-focused assessment of factors likely to impact on adherence with particular attention towards recent changes:
	  • Status of caregiver, financial stability, housing, intimate relationships
	  • School and achievement
	  • Substance abuse (child, caretaker, family members)
	  • Mental health and behavior
	  • Child/youth and caretaker beliefs towards antiretroviral therapy
	  • Disclosure status (to
		• Address competing needs through appropriate social services.
		• Address and treat concomitant mental illness and behavioral disorders. Initiate disclosure discussions with family/child.
		• Consider need for child protection services and alternate care settings when necessary.

Assessment	Method	Intervention
	child and others)	
Pharmacokinetics and Dosing	1. Recalculate doses for individual medications using weight or body surface area. 2. Identify concomitant medications including prescription, over-the-counter and recreational substances; assess for drug-drug interactions. 3. Consider drug levels for specific antiretroviral drugs (see "Role of Therapeutic Drug Monitoring in Management of Treatment Failure").	• Adjust drug doses. • Discontinue or substitute competing medications. • Reinforce applicable food restrictions.
Resistance Testing	1. Genotypic and phenotypic resistance assays (see "Antiretroviral Drug Resistance Testing"). 2. Tropism assay, as appropriate.	

Approach to the Management of Antiretroviral Treatment Failure

Working Group Recommendations

- The causes of treatment failure need to be assessed and addressed. These include drug resistance, poor absorption of medications, poor adherence, inadequate dosing and drug-drug interactions.
- When deciding how to treat a child with treatment failure, a clinician should consider the likelihood of achieving durable suppression based on the prior treatment history, drug resistance, drug potency, likelihood of adherence, and the future options available should durable suppression not be achieved. In addition, the future availability and timing of novel agents should be considered.
- Children who experience treatment failure should be managed in collaboration with a pediatric HIV specialist.

General

Once the causes of failure have been identified and addressed, the child should be assessed to determine whether a change in the antiretroviral regimen is necessary. This will depend on the urgency and likelihood of achieving and sustaining an undetectable plasma viral load. The immediacy of implementing a more effective treatment regimen depends on the immunologic status of the child but is most necessary for patients with clinical disease progression or clinical

failure. The likelihood of achieving and maintaining undetectable plasma viral load depends on the extent of drug resistance, the number and quality of available agents that are active against the child's virus, and the likelihood of adherence to the new regimen.

Timing of Initiation of a New Regimen: Relative Importance of Virologic Suppression and Immunologic Improvement

Because immunologic improvement typically results from achieving undetectable plasma viral load, the urgency of re-establishing virologic suppression depends on the clinical and immunologic status of a child. For example, for older children or adolescents with very low CD4 cell counts (e.g., <200 cells/mm^3), a change in therapy may be critical to prevent further immunologic decline or clinical disease progression, and is strongly recommended. A patient with less immunosuppression may not be at significant risk of clinical disease progression in the near future, so an immediate change in therapy is less urgent. However, continued treatment of a child with persistently detectable viremia increases the risk of immunologic or clinical disease progression and leads to further accumulation of resistance mutations, possibly further limiting future treatment options.

Likelihood of Viral Suppression Below the Limit of Detection Using the Most Sensitive Assay

When deciding whether to change a child's antiretroviral regimen, a clinician must assess whether such a change is likely to achieve significantly better virologic control than the current regimen. While complete virologic suppression should be the goal, this may not always be achievable in HIV-infected children. Clinical benefit may be observed with decrements in HIV RNA levels that do not result in undetectable levels. However, failure to maximally suppress plasma viral load is associated with an increased probability of acquiring mutations associated with resistance. Anticipating and minimizing toxicities is central to the clinician-patient discussion. The likelihood of adherence to a new regimen plays a significant role in determining whether or not to change an antiretroviral regimen; if a child is unlikely to adhere to a new regimen, resistance will develop and sustainable virologic suppression will not be achieved. Although studies differ on the exact predictors of adherence, several contributing factors have been noted. These include medication characteristics, psychosocial stressors, health beliefs, and prior adherence to medication (see the section Adherence to Antiretroviral Therapy in HIV-Infected Children and Adolescents for more detail). Importantly, the pediatric patient's adherence to antiretroviral therapy may change over time as they move through progressive developmental stages, and any changes in these risk factors can occur rapidly and unexpectedly. Thus, a clinician may choose to target a new antiretroviral regimen to start at a time when the child is most likely to adhere to this regimen for a sustained period.

Refer to the original guideline document for a discussion of categories of children with treatment failure and approaches to consider in each category, including the following situations:

- No viral resistance identified
- Viral resistance to current therapy

- Extensive drug resistance such that two fully active agents cannot be identified or administered

Choice of Next Antiretroviral Regimen for Treatment Failure with Evidence of Drug Resistance

Working Group Recommendations

- Antiretroviral regimens should be chosen based on treatment history and drug-resistance testing, including past and current resistance test results.
- Ideally, use three fully active antiretroviral medications in the new regimen, assessing anticipated antiretroviral activity based on past treatment history and resistance test results.
- Interpretation of resistance test results showing complex combinations of mutations and assessment of future treatment options should be made in collaboration with a pediatric HIV specialist.
- Use of novel agents with limited available pharmacokinetic and/or safety data in pediatric populations should be undertaken only in collaboration with a pediatric HIV specialist.

General

After carefully reaching a decision that a change in therapy is needed, the clinician should attempt to identify at least two but preferably three fully active antiretroviral agents on the basis of resistance testing, prior ARV exposure, acceptability to the patient, and likely adherence. This often requires the use of one or more new drug classes. Substitution or addition of a single drug to a failing regimen should be avoided as this approach is unlikely to achieve and sustain an undetectable plasma viral load, and frequently will result in additional drug resistance. A drug may be "new" to the patient but have diminished antiviral potency due to the presence of drug mutations that confer cross-resistance within a drug class. In children who are changing therapy due to occurrence or progression of abnormal neurodevelopment, the new treatment regimen should include agents (such as zidovudine) that are known to achieve higher levels within the central nervous system.

A change to a new regimen must include an extensive discussion of treatment adherence and potential toxicity with the patient in an age- and developmentally-appropriate manner and with the patient's caregivers. The clinician must recognize that conflicting requirements of some medications with respect to food and concomitant medication restrictions may complicate coordination of a regimen. Timing of medication administration is particularly important to ensure adequate antiretroviral drug exposures throughout the day. Palatability, pill size, pill number, and dosing frequency all need to be considered when choosing a new regimen.

Choice of Therapy with Viral Resistance to Current Therapy: Goal of Complete Virologic Suppression

Determination of a new regimen with the best chance for complete virologic suppression in children who have already experienced treatment failure should be made in collaboration with a pediatric HIV specialist. Antiretroviral regimens should be chosen based on treatment history and drug resistance testing to optimize antiretroviral drug potency in the new regimen. A general strategy for regimen change is shown in the table below, although, as additional agents are licensed and studied for use in children, newer strategies, better tailored to the needs of each patient may be constructed.

Table. Options for Regimens with at Least Two Fully Active Agents Following Failure of Antiretroviral Regimen with Evidence for Viral Resistance to Therapy with Goal of Virologic Suppression*

Prior Regimen	Recommended Change
2 NRTIs + NNRTI	• 2 NRTIs (based on resistance testing) + PI
2 NRTIs + PI	• 2 NRTIs (based on resistance testing) + NNRTI • 2 NRTIs (based on resistance testing) + alternative PI (with low-dose ritonavir boosting if possible, based on resistance testing) • NRTI(s) (based on resistance testing) + NNRTI + alternative PI (with low-dose ritonavir boosting if possible, based on resistance testing)
3 NRTIs	• 2 NRTIs (based on resistance testing) + [NNRTI *or* PI] • NRTI(s) (based on resistance testing) + [NNRTI + PI]
Failed regimens including NRTI, NNRTI, PI	• >1 NRTI (based on resistance testing) + a newer PI (with low-dose ritonavir, based on resistance testing) • >1 NRTI + dual boosted PI (lopinavir/r +saquinavir, lopinavir/r + atazanavir) (consider adding either one or more of enfuvirtide, etravirine, or an integrase inhibitor) • NRTI(s) + ritonavir boosted, potent PI (based upon resistance testing) + etravirine • NRTI(s) + ritonavir boosted, potent PI (based upon resistance testing) + enfuvirtide and/or CCR5 antagonist and/or integrase inhibitor • If patient refuses PI and/or ritonavir boosting: NRTI(s) + enfuvirtide and/or integrase inhibitor and/or CCR5 antagonist

* Antiretroviral regimens should be chosen based on treatment history and drug resistance testing to optimize antiretroviral drug effectiveness in the second regimen. This is particularly important in selecting NRTI components of an NNRTI-based regimen where drug resistance may occur rapidly to the NNRTI if the virus is not sufficiently sensitive to the NRTIs. Regimens should contain at least two, but preferably three, fully active drugs for durable, potent virologic suppression.

Choice of Therapy with Extensive Drug Resistance Such That Two Fully Active Agents Cannot Be Identified or Administered

The creation of an effective and sustainable therapeutic regimen may not be possible with currently available agents due to lack of potency in the face of extensive drug resistance, or the patient's inability to adhere to, or tolerate, combination antiretroviral therapy. In such cases, non-suppressive regimens (or "holding regimens") are sometimes used with the overall objective of preventing clinical and immunological deterioration while waiting for the availability of additional active drugs which can be used to design a regimen that is expected to achieve undetectable plasma viral load. This approach should be regarded as acceptable but not ideal. These patients should be followed more closely than patients with stable virologic status, and the potential to successfully initiate a fully suppressive antiretroviral regimen should be reassessed at every opportunity.

Even when NRTI drug resistance mutations are present, there can be immunologic and clinical benefit despite persistent viremia when patients are treated with lamivudine monotherapy or when they are treated with lamivudine or emtricitabine in combination with one or more other NRTIs, such as zidovudine, stavudine, abacavir, or tenofovir.

Since the newer NNRTI etravirine retains activity against nevirapine- or efavirenz-resistant virus in the presence of a limited number of NNRTI resistance-associated mutations, efavirenz or nevirapine should not be continued as part of a failing regimen if NNRTI resistance is documented.

Continued use of a PI in the face of persistent viremia can lead to accumulation of additional mutations conferring resistance to that PI as well as other, newer PIs. Such acquisition of additional PI drug resistance occurs slowly, especially if the viral load is relatively low. However, continued PI use, in the presence of resistance, may limit viral replication and be beneficial to some patients.

In general, every effort should be made to avoid adding a single, new, fully active agent to these "holding" non-suppressive regimens, since such use of a single fully active agent will quickly lead to diminished activity of that agent. When clinical or immunologic deterioration occurs in such cases, it is often appropriate to use investigational agents or agents approved for older age groups as a second fully active drug in the new regimen (see The Use of Antiretroviral Agents Not Approved for Use in Children below).

The Use of Antiretroviral Agents not Approved for Use in Children

Working Group Recommendations

- Some children with HIV need to use antiretrovirals that are not yet approved for their age range because many of the recently-approved, more convenient and potent agents are ready for approval in adults before data are available in children.
- This "off-label" use of antiretrovirals can be risky, as dosing recommendations have not yet been made and often cannot be inferred from a simple

calculation using the adult dose and the child's weight.
- Off-label use of antiretrovirals should always be done in collaboration with a pediatric HIV specialist, who may have access to unpublished data about safety and pharmacokinetics of these agents.
- Whenever possible, use of antiretrovirals that are not yet FDA-approved for children should be done in the context of clinical trials that can generate the data needed for pediatric approval.

Role of Therapeutic Drug Monitoring in Management of Treatment Failure

Therapeutic drug monitoring (TDM) is the term used to describe the use of plasma drug concentration measurements as part of a strategy to optimize drug dosing to minimize toxicity and maximize treatment benefit. TDM can be considered for use in antiretroviral treatment because:

- There is high interpatient variability in antiretroviral exposure (plasma drug concentrations) using standard recommended doses
- Low drug exposure can lead to suboptimal virologic response to therapy
- High plasma concentrations can be associated with increased risk of drug toxicity

See Table 15 in the original guideline document for suggested minimum target trough concentrations for persons with wild-type HIV.

Discontinuation or Interruption of Therapy

Discontinuation of antiretroviral therapy may be indicated in some situations, including serious treatment-related toxicity, acute illnesses or planned surgeries that preclude oral intake, lack of available medication, or patient or parent request. While these events are usually unplanned, purposeful discontinuation of therapy has been widely used in the adult population to reduce toxicity, costs, and drug-related failure associated with antiretroviral therapy. At this time, there are minimal data in infants, children, and adolescents about planned structured treatment interruptions (STIs). Thus, STI should not be attempted in children or adults outside of a clinical trial setting. The discussion in the original guideline document provides general guidance for the interruption of antiretroviral therapy and the risks and benefits in specific situations.

When a short-term therapy interruption is indicated, all antiretroviral therapy should be stopped at the same time in most cases. This can be problematic with agents with a long half-life. Stopping agents with different half-lives at the same time can result in functional monotherapy with the drug with the longest half-life. This is particularly concerning in the case of the NNRTIs efavirenz and nevirapine.

Antiretroviral Drug Resistance Testing

Working Group Recommendations

- Antiretroviral drug resistance testing is recommended prior to initiation of

therapy in all treatment-naïve children.

- Antiretroviral drug resistance testing is recommended prior to changing therapy for treatment failure.
- Resistance testing in the setting of virological failure should be obtained when patients have a viral load >1,000 copies/mL while still on the failing regimen, or within 4 weeks of discontinuation of the regimen.
- The absence of detectable resistance to a drug does not insure that its use will be successful, especially if it shares cross-resistance with drugs previously used. In addition, current resistance assays are not sensitive enough to fully exclude the presence of resistant virus. Thus, the history of past use of antiretroviral agents is important in making decisions regarding the choice of new agents for patients with virologic failure.
- Viral Coreceptor (tropism) assays should be used whenever the use of a CCR5 antagonist is being considered. Tropism assays should also be considered for patients who demonstrate virologic failure while receiving therapy that contains a CCR5 antagonist.
- Consultation with a specialist in pediatric HIV infection is recommended for interpretation of resistance assays when considering starting or changing an antiretroviral regimen in a pediatric patient.

HIV replication is a continuous process in most untreated patients, leading to the daily production of billions of viral particles. The goal of antiretroviral therapy is to suppress HIV replication as rapidly and fully as possible, indicated by a reduction in plasma HIV RNA to below the limit of detection of the most sensitive assays available (<50–70 copies/mL). Unfortunately, mutations in HIV RNA readily arise during viral replication since HIV reverse transcriptase is a highly error-prone enzyme. Consequently, ongoing replication in the presence of antiretroviral drugs readily and progressively selects for strains of HIV with mutations that confer drug resistance.

Drug resistance detection methods vary depending on the class of antiretroviral agents. Both genotypic assays and phenotypic assays are used to detect the presence of virus that is resistant to inhibitors of the HIV reverse transcriptase (RT) and protease (PR). Viral coreceptor (tropism) assays, a form of phenotypic assay, have been successfully employed in detecting the presence of virus with tropism that will (R5 tropism) or will not (X4 or mixed tropism) respond to CCR5 antagonists. Clinical experience with testing for viral resistance to other agents is more limited, but genetic mutations associated with resistance to integrase strand transfer inhibitors have been identified, and a commercial phenotypic assay is available for evaluation of resistance to fusion inhibitor enfuvirtide (T20). Experience is also limited with the use of commercially available genotypic and phenotypic assays in the evaluation of drug resistance in patients infected with non-B subtypes of HIV.

Refer to the original guideline document for further discussion on the use of resistance assays and their limitations.

Managing Complications of HIV Infection

The Pediatric Antiretroviral Treatment Guidelines includes the supplements Managing Complications of HIV Infection and Adverse Drug Effects. These supplements contain guidelines on two important issues in pediatric HIV infection—nutrition and pain management—as well as separate sections on specific adverse drug effects, including lactic acidosis, hepatic toxicity, fat maldistribution and body habitus changes, hyperlipidemia, hyperglycemia, osteopenia, hematological complications, and hypersensitivity reactions and skin rashes. The United States Public Health Service (USPHS), HIV Medicine Association of the Infectious Diseases Society of America (IDSA), and Pediatric Infectious Disease Society jointly developed and published guidelines for the prevention and treatment of opportunistic infection in HIV-exposed and infected children, as well as adults. These guidelines are available online at the AIDSinfo Web site. (See also the National Guideline Clearinghouse [NGC] summary Treating Opportunistic Infections Among HIV-exposed and Infected Children).

Definitions:

Guideline recommendations for drugs or drug combinations for use in treatment-naïve children are classified in one of several categories as follow:

- **Preferred**: Drugs or drug combinations are designated as preferred for use in treatment-naïve children when clinical trial data in children or, more often, in adults have demonstrated optimal efficacy and durability with acceptable toxicity and ease of use, and studies have been performed to demonstrate safety and surrogate marker efficacy in children; additional considerations are listed in the original guideline document.
- **Alternative**: Drugs or drug combinations are designated as alternatives for initial therapy when clinical trial data in children or adults show efficacy but there are disadvantages compared to preferred regimens in terms of more limited experience in children; the extent of antiviral efficacy or durability is less well defined in children or less than a preferred regimen in adults; there are specific toxicity concerns; or there are dosing, formulation, administration, or interaction issues for that drug or regimen.
- **Use in Special Circumstances**: Some drugs or drug combinations are recommended only for use in special circumstances, when preferred or alternative drugs cannot be used.
- **Not Recommended**: A list of drugs and drug combinations that are not recommended for initial therapy in children is shown in Table 4 in the original guideline document. These drugs and drug combinations are not recommended either because of inferior virologic response, potential serious safety concerns (including potentially overlapping toxicities), or pharmacologic antagonism.
- **Insufficient Data to Recommend**: There are a number of drugs and drug combinations that are approved for use in adults that do not have pharmacokinetic or safety data available in children, or for which such data are too limited to make a recommendation for use for initial therapy in children. Some of these drugs and drug combinations may be appropriate for consideration in the management of the treatment-experienced child (see "Antiretroviral Treatment Failure in Infants, Children, and Adolescents" in the original guideline document).

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

Although prospective, randomized, controlled clinical trials offer the best evidence for formulation of guidelines, most antiretroviral drugs are approved for use in pediatric patients based on efficacy data from clinical trials in adults, with supporting pharmacokinetic and safety data from phase I/II trials in children. Additionally, efficacy has been defined in most adult trials based on surrogate marker data, as opposed to clinical endpoints. For the development of these guidelines, the Working Group reviewed relevant clinical trials published in peer-review journals or in abstract form, with attention to data from pediatric populations when available.

Recommendations are based on published and unpublished data regarding the treatment of human immunodeficiency virus (HIV) infection in infants, children, and adults and, when no definitive data were available, the clinical experience of the Working Group members.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate implementation of the recommendations will help to achieve the following goals of antiretroviral therapy for human immunodeficiency virus (HIV)-infected infants, children, and adolescents:

- Reducing HIV-related mortality and morbidity
- Restoring and preserving immune function
- Maximally and durably suppressing viral replication
- Minimizing drug-related toxicity
- Maintaining normal physical growth and neurocognitive development
- Improving quality of life

Refer to Table 5 "Advantages and Disadvantages of Different Nucleoside or Nucleotide Analogue Reverse Transcriptase Inhibitor (NRTI, NtRTI) Backbone Combinations for Use in Highly Active Antiretroviral Combination Regimens for Initial Therapy in Children" in the original guideline document.

Refer to Table 6 "Advantages and Disadvantages of Different Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) for Use in Highly Active Antiretroviral Combination Regimens for Initial Therapy in Children" in the original guideline document.

Refer to Table 7 "Advantages and Disadvantages of Different Protease Inhibitors (PIs) for Use in Highly Active Antiretroviral Combination Regimens for Initial Therapy in Children" in the original guideline document.

Refer to Table 8 "Advantages and Disadvantages of Entry Inhibitors for Use in Highly Active Antiretroviral Combination Regimens" in the original guideline document.

Refer to Table 9 "Advantages and Disadvantages of Integrase Inhibitors for Use in Highly Active Antiretroviral Combination Regimens" in the original guideline document.

POTENTIAL HARMS

The possibility of toxicities such as lipodystrophy, dyslipidemia, glucose intolerance, osteopenia, and mitochondrial dysfunction with prolonged therapy is a concern. These concerns are particularly relevant because life-long administration of therapy may be necessary. See Appendix B "Characteristics of Available Antiretroviral Drugs" in the original guideline document and the companion document "Supplement III: Adverse Drug Effects" for major toxicities and adverse events associated with the antiretroviral drugs.

When drug concentrations are subtherapeutic, either because of inadequate dosing, poor absorption, or incomplete adherence, antiretroviral drug resistance can develop rapidly, particularly in the setting of high levels of viral replication in young infants. It is particularly critical that the importance of adherence to the treatment is fully discussed with the caregivers, and that potential problems are identified and resolved prior to initiation of therapy, even if this delays starting treatment.

Refer to Table 5 "Advantages and Disadvantages of Different Nucleoside or Nucleotide Analogue Reverse Transcriptase Inhibitor (NRTI, NtRTI) Backbone Combinations for Use in Highly Active Antiretroviral Combination Regimens for Initial Therapy in Children" in the original guideline document.

Refer to table 6 "Advantages and Disadvantages of Different Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) for Use in Highly Active Antiretroviral Combination Regimens for Initial Therapy in Children" in the original guideline document.

Refer to Table 7 "Advantages and Disadvantages of Different Protease Inhibitors (PIs) for Use in Highly Active Antiretroviral Combination Regimens for Initial Therapy in Children" in the original guideline document.

Refer to Table 8 "Advantages and Disadvantages of Entry Inhibitors for Use in Highly Active Antiretroviral Combination Regimens" in the original guideline document.

Refer to Table 9 "Advantages and Disadvantages of Integrase Inhibitors for Use in Highly Active Antiretroviral Combination Regimens" in the original guideline document.

CONTRAINDICATIONS

CONTRAINDICATIONS

Refer to Appendix B "Characteristics of Available Antiretroviral Drugs" in the original guideline document and the companion document "Supplement III: Adverse Drug Effects" for information on agents that are contraindicated or should not be used in certain clinical situations.

Refer to Table 4 "Antiretroviral Regimens or Components that Should Not Be Offered for Treatment of Human Immunodeficiency Virus (HIV) Infection in Children" in the original guideline document.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- As these guidelines were developed for the United States, they may not be applicable in other countries. The World Health Organization provides guidelines for resource-limited settings at http://www.who.int/hiv/pub/guidelines/art/en/index.html.
- These recommendations represent the current state of knowledge regarding the use of antiretroviral drugs in children, and are based on published and unpublished data regarding the treatment of HIV infection in infants, children, and adults and, when no definitive data were available, the clinical expertise of the Working Group members. The Working Group intends the guidelines to be flexible and not to replace the clinical judgment of experienced health care providers.
- The Treatment Recommendations provide general guidance for decisions related to treatment of HIV-infected children, and flexibility should be exercised according to a child's individual circumstances. Guidelines for treatment of HIV-infected children are evolving as new data from clinical trials become available. Although prospective, randomized, controlled clinical trials offer the best evidence for formulation of guidelines, most antiretroviral drugs are approved for use in pediatric patients based on efficacy data from clinical trials in adults, with supporting pharmacokinetic and safety data from phase I/II trials in children. Additionally, efficacy has been defined in most adult trials based on surrogate marker data, as opposed to clinical endpoints. For the development of these guidelines, the Working Group reviewed relevant clinical trials published in peer-reviewed journals or in abstract form, with attention to data from pediatric populations when available.
- The care of HIV-infected children is complex and evolving rapidly as results of new research are reported and new antiretroviral drugs and newer classes of drugs are approved. Clinical trials to define appropriate drug dosing and toxicity in children ranging in age from infancy to adolescence are critical as new drugs become available. As additional antiretroviral drugs become approved and optimal use of these drugs in children becomes better understood, the Working Group will modify these guidelines. It should be noted that guidelines are only a starting point for medical decision making, and are not meant to supersede the judgment of clinicians experienced in the care of HIV-infected children. Because of the complexity of caring for HIV-infected children, health care providers with limited experience in the care of these patients should seek consultation with an expert in such care.
- Use of antiretrovirals in pediatric patients is evolving rapidly. These guidelines are updated regularly to provide current information. The most recent information is available at the AidsInfo Web site.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Foreign Language Translations
Patient Resources
Personal Digital Assistant (PDA) Downloads
Pocket Guide/Reference Cards
Slide Presentation

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the use of antiretroviral agents in pediatric HIV infection. Bethesda (MD): U.S. Department of Health and Human Services; 2008 Feb 23. 139 p. [460 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

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Health Resources and Services Administration - Federal Government Agency [U.S.]
National Institutes of Health (U.S.) - Federal Government Agency [U.S.]
National Pediatric and Family HIV Resource Center - Private Nonprofit Organization

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GUIDELINE COMMITTEE

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- InfraCare (Consultant)
- Mpex Pharmaceuticals (Consultant)
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GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the use of antiretroviral agents in pediatric HIV infection. Bethesda (MD): U.S. Department of Health and Human Services; 2008 Jul 29. 134 p.

GUIDELINE AVAILABILITY

Electronic copies: Available from the AIDSinfo Web site.

The guideline is also available for Palm OS or Pocket PC download from the AIDSinfo Web site.

Print copies: Available from the Centers for Disease Control and Prevention, National Prevention Information Network (NPIN), P.O. Box 6003, Rockville, MD 20850. Telephone: (800) 458-5231, TTY (800)-243-7012 International number (301)-562-1098. Web site: http://www.cdcnpin.org. Requests for print copies can also be submitted via the AIDSinfo Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Supplement I: pediatric antiretroviral drug information. Bethesda (MD): Department of Health and Human Services, Public Health Service (PHS), Centers for Disease Control and Prevention (CDC); 2001 Dec 14 (revised 2009 Feb 23). 67 p. Available in Portable Document Format (PDF) from the AIDSinfo Web site. Also available for Palm OS or Pocket PC download from the AIDSinfo Web site.
- Supplement II: managing complications of HIV infection in HIV-infected children on antiretroviral therapy. Bethesda (M D): Department of Health and Human Services, Public Health Service (PHS), Centers for Disease Control and Prevention (CDC); 2008 Feb 28. 18 p. Available in Portable Document Format (PDF) from the AIDSinfo Web site. Also available for Palm OS or Pocket PC download from the AIDSinfo Web site.
- Supplement III: adverse drug effects. Bethesda (MD): Department of Health and Human Services, Public Health Service (PHS), Centers for Disease Control and Prevention (CDC); 2008 Feb 28. 58 p. Available in Portable Document Format (PDF) from the AIDSinfo Web site. Also available for Palm OS or Pocket PC download from the AIDSinfo Web site.
- Antiretroviral Pocket Reference Cards. Antiretroviral agents pediatric edition. AIDS Educational and Training Center (AETC) 2008 Mar. Available from the AETC Web site.
- Mofenson LM, Oleske J, Serchuck L, Van Dyke R, Wilfert C. Treating opportunistic infections among HIV-exposed and infected children: recommendations from CDC, the National Institutes of Health, and the Infectious Diseases Society of America. Clin Infect Dis. 2005 Feb 1;40 Suppl 1:S1-84. Available in Portable Document Format (PDF) from the AIDSinfo Web site.

The following PowerPoint slide sets based on the "Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection" are also available:

- Guidelines for use of antiretroviral agents in pediatric HIV infection: comprehensive slide set. AIDS Education and Training Centers (AETC) National Resource Center. 2009 Feb 23. 90 slides. Available from the AETC Web site.
- Pediatric antiretroviral guidelines: pain management. AIDS Education and Training Centers (AETC) National Resource Center. 2008 Mar 24. 26 slides. Available from the AETC Web site.

- Pediatric antiretroviral guidelines: nutritional care. AIDS Education and Training Centers (AETC) National Resource Center. 2005 Mar 24. 20 slides. Available from the AETC Web site.
- Pediatric antiretroviral guidelines: adverse drug effects. AIDS Education and Training Centers (AETC) National Resource Center. 2007 Sep 11. 48 slides. Available from the AETC Web site.

The following tools are also available:

- AIDSinfo's Drug Database. Available in English and Spanish from the AIDSinfo Web site. See the related QualityTool summary on the Health Care Innovations Exchange Web site.
- AIDSinfo's HIV/AIDS Glossary, 4th ed. Available for PDA, in HTML format, and in Portable Document Format (English and Spanish) from the AIDSinfo Web site. See the related QualityTool summary on the Health Care Innovations Exchange Web site.
- A comprehensive Spanish-language Web site featuring information about HIV treatment and clinical trials is available at http://aidsinfo.nih.gov/infoSIDA/.

PATIENT RESOURCES

The following is available:

- HIV during pregnancy, labor and delivery, and after birth. Fact sheets. Rockville (MD): Department of Health and Human Services (DHHS); 2008 Jan. 9 p. Available in Portable Document Format (PDF) from the AIDSinfo Web site.

Print copies: Available from the Centers for Disease Control and Prevention, National Prevention Information Network (NPIN), P.O. Box 6003, Rockville, MD 20850. Telephone: (800) 458-5231, TTY (800)-243-7012 International number (301)-562-1098. Web site: http://www.cdcnpin.org.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

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